REMARKS

Claims 113 to 116, 118 to 121, 124 to 127, 130,131, 133 to 135 and 142 to 143 and 145 to 149 have been canceled. New claims 150 to 256 have been added. The amendments to the claims are discussed below.

No new matter is added by any of the foregoing amendments to the claims.

Applicants acknowledge the Examiner's withdrawal of the previous rejections of claim 113 to 116, 122 to 123 and 144 under 35 U.S.C. § 112, first paragraph

Applicants have also noted the Examiner's conclusion that claims 145 to 149 appear to be free of the prior art, but are objected for being dependent from a rejected independent claim.

Amendment of the Claims

Claims 150 to 256 of the present application are directed to:

1. methods of treating a subject with a B-cell malignancy comprising administering to the subject a therapeutically effective dose of a composition comprising a therapeutically effective dose of a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate in which the anti-CD22 antibody comprises:
    a. a light chain variable region comprising SEQ ID NO:19 and a heavy chain variable region comprising SEQ ID NO:27 (**Claims 150 to 172**);
    b. a light chain variable region comprising SEQ ID NO:28 and a heavy chain variable region comprising SEQ ID NO:30 (**Claims 173 to 195**);
    c. SEQ ID NO: 1 for CDR-H1, SEQ ID NO: 2 or SEQ ID NO: 13 or SEQ ID NO: 15 or SEQ ID NO: 16 or residues 50-65 of SEQ ID NO: 27 for CDR-H2, SEQ ID NO: 3 for CDR-H3, SEQ ID NO: 4 for CDR-L1, SEQ ID NO: 5 for CDR-L2 and SEQ ID NO: 6 for CDR-L3 (**Claims 196 to 218**); or
    d. a light chain variable region comprising SEQ ID NO:7 and a heavy chain variable region comprising SEQ ID NO:8 (**Claims 219 to 241**); and

2. methods of treating a subject with aggressive lymphomas comprising administering to the subject a therapeutically effective dose of a composition comprising a therapeutically effective dose of a monomeric calicheamicin derivative-anti-CD22 antibody conjugate, which comprises a calicheamicin derivative functionalized with 3-mercapto-3-methyl butanoyl hydrazide and an anti-CD22 antibody comprising SEQ ID NO:1 for CDR-H1, SEQ ID NO: 2 or SEQ ID NO:13 or SEQ ID NO:15 or SEQ ID NO:16 or residues 50-65 of SEQ ID NO:27 for CDR-H2, SEQ ID NO:3 for CDR-H3, SEQ ID NO:4 for CDR-L1, SEQ ID NO:5 for CDR-L2, and SEQ ID NO:6 for CDR-L37 (**Claims 242 to 256**).

These claims are supported by the application as filed. Particular amendments not previously presented are described below.

A. New Claims 151, 174, 197 and 220

Claims 151, 174, 197 and 220 recite a biologically active antibody fragment that is a Fab, a modified Fab, Fab', F(ab')2 or Fv, or a heavy chain monomer or dimer. Support for this amendment can be found in the specification at page 22, lines 14-16 and page 24, lines 20-26.

B. New Claims 154 to 157, 177 to 180, 200 to 203, 223 to 226 and 244 to 247

Claims 154, 177, 200, 223 and 244 recite that the donor residues are at positions 1, 28, 48, 72 and 97 in SEQ ID NO:8. Claims 155, 178, 201, 224 and 245, which depend respectively from claims 154, 177, 200. 223 and 244, recite that the antibody further comprises donor residues at positions 68 and 70 in SEQ ID NO: 8. These claims are supported by the application as filed. Page 23, line 7 to page 24, line 25, provides a general description about CDR-grafted antibodies and how they are made, including a general description of the exemplified CDR-grafted humanized anti-CD22 antibody. Page 50, line 5 to page 51, line 10, describe the CDR-grafting of mouse 5/44 variable regions of the light and heavy chains whose sequences are provided in Figures 2 and 3, respectively, and in SEQ ID NOS: 7 and 8, respectively, onto human frameworks to produce the exemplified CDR-grafted anti-CD22 antibody.

For the grafting of the heavy chain, the sequence of the human sub-group I germline framework VH1-3,DP7, which is presented in SEQ ID NO:21, was used as an acceptor framework. The framework 4 acceptor sequence was derived from the human J-region germline sequence JH4, which is presented in SEQ ID NO:22. Figure 6 provides a comparison of the murine 5/44 heavy chain with the acceptor framework sequences and shows differences at 22 positions. Using the same strategy as for the light chain described on page 50, lines 15-29, an analysis was made of the potential of the murine residue to contribute to antigen binding, and if the murine residue was considered important and sufficiently different from the human residue, then that murine residue was retained. In Figure 6, the sequence given for heavy chains gH1, gH4, gH5, gH6 and gH7 shows that murine residues E (glutamic acid, Glu), R (arginine, Arg), I (isoleucine, Ile), A (alanine, Ala), and T (threonine, Thr) at positions 1, 28, 48, 72 and 97, respectively, were retained. When these five amino acids are compared with the amino acid sequence in SEQ ID NO:8, these amino acids appear at positions 1, 28, 48, 72 and 97 in SEQ ID NO:8 and are considered the donor residues as identified in claims 154, 177, 200, 223 and 244.

In claims 155, 178, 201, 224 and 245, which depend respectively from claims 154, 177, 200, 223 and 244, two additional murine residues at positions 68 and 70 in the sequence, A (alanine, Ala) and L (leucine, Leu), respectively, are retained in the sequences for heavy chains gH1, gH4 and gH6. When these two amino acids are compared with the amino acid sequence in SEQ ID NO:8, these amino acids appear at positions 68 and 70 in SEQ ID NO:8 and are considered the donor residues as identified in claims 154, 177, 200, 223 and 244.

Turning next to claims 156, 179, 202, 225 and 246, these claims recite that the light chain donor residues are at positions 2, 4, 42, 43, 50 and 65 in SEQ ID NO:7, which is supported by the application as filed. As noted above, page 23, line 7 to page 24, line 25, provides a general description about CDR grafted antibodies and how they are made, including a general description of the exemplified CDR-grafted humanized anti-CD22 antibody. Page 50, line 5 to page 51, line 10 describes the CDR-grafting of mouse 5/44 variable regions of the light and heavy chains whose sequences are provided in Figures 2 and 3, respectively, and in SEQ ID NOS:7 and 8, respectively, onto human frameworks to produce the exemplified CDR-grafted anti-CD22 antibody. Claims 157, 180, 203, 226, and 247, which depend respectively from

claims 156, 180, 202, 225 and 246, have been amended to add the sequence listing identifier SEQ ID NO:7.

For the grafting of the light chain, the sequence of the human VK sub-group I germline framework O12,DPK9, which is presented in SEQ ID NO:17, was used as an acceptor framework. The framework 4 acceptor sequence was derived from the human J-region germline sequence JK1, which is presented in SEQ ID NO:18. Figure 5 provides a comparison of the murine 5/44 light chain with the acceptor framework sequences and shows differences at 27 positions. Using the strategy described on page 50, lines 15-29, an analysis was made of the potential of the murine residue to contribute to antigen binding, and if the murine residue was considered important and sufficiently different from the human residue, then that murine residue was retained. In Figure 5, the sequences given for light chains gL1 and gL2 show that murine residues V (valine, Val), V (valine, Val), L (leucine, Leu), H (histidine, His), Q (glutamine, Gln), and D (aspartic acid, Asp) at positions 2, 4, 42, 43, 50 and 65, respectively, were retained. When these six amino acids are compared with the amino acid sequence in SEQ ID NO:7, these amino acids appear at positions 2, 4, 42, 43, 50 and 65 in SEQ ID NO:7 and are considered the donor residues as identified in claims 156, 179, 202, 225 and 246.

When the application was initially drafted, the residues in the antibody variable domain, which is comprised of a heavy chain and light chain, were numbered using the conventional numbering system created by Kabat et al., published in 1987 in the book Sequences of Proteins of Immunological Interest, US Department of Health and Human Services, NIH, USA. See the position numbers given on page 9, lines 12-17 and lines 18-23. The Kabat residue designations do not always correspond directly with the linear numbering of the amino acid residues in an amino acid sequence. The actual linear amino acid sequence may contain fewer or additional amino acids than in the strict Kabat numbering corresponding to a shortening of, or insertion into, a structural component, whether framework or complementarity determining region (CDR), of the basic variable domain structure. Applicants did not notice the difference in the position numbers of the amino acid residues between the Kabat numbered and linear numbered residues when the application was filed. As indicated above, the correct position numbers are given in the new claims based on the actual linear numbering of the amino acids using Figures 5 and 6 and the sequences provided therein, and in the Sequence Listing. Given the support in

the application, a person of ordinary skill in the art would deduce that the linear numbering of the residues was incorrect and would make the corrections that applicants now seek to make.

Applicants respectfully submit that no new matter is added by these amendments to the claims.

Rejections Under 35 U.S.C. §102(b)

A. First Rejection Under 35 U.S.C. §102(b)

The Examiner has maintained his rejection of claim 113 under 35 U.S.C. §102(b) as being anticipated by Ghetie et al. (Blood 1992; 80:2315-2320), as evidenced by Newton et al. (Blood 2001; 97: 528-535). Specifically, the Examiner states that Ghetie et al. teach a method of treating a lymphoma, comprising administering a therapeutically effective amount of a cytotoxic drug/carrier conjugate referred to as RFB4-dgA, where deglycosylated ricin A chain is the cytotoxic drug and the carrier is an antibody directed against the CD22 antigen. The Examiner further states that Ghetie et al. teach a method of treating disseminated Daudi lymphoma by administering a therapeutically effective amount of the RFB4-dgA conjugate with an anti-CD19 antibody. The Examiner cites Newton et al. to show that Daudi lymphoma is a B cell malignancy.

Claim 113 has been replaced with new claim 150, which is directed to a method of treatment of a subject with a B-cell malignancy comprising administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate in which the anti-CD22 antibody comprises a light chain variable region comprising SEQ ID NO:19 and a heavy chain variable region comprising SEQ ID NO:27. Ghetie et al. does not teach a method of treating a subject with a B-cell malignancy that comprises administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate in which the anti-CD22 antibody comprises a light chain variable region comprising SEQ ID NO:19 and a heavy chain variable region comprising SEQ ID NO:27. The composition used in the claimed methods is not described in Gehtie et al. nor is it inherent from Gehtie et al.'s teachings. Applicants submit that Ghetie et al. does not teach every element of the claimed invention.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claim 113 as anticipated under 35 U.S.C. §102(b).

B. Second Rejection Under 35 U.S.C. §102(b)

The Examiner has maintained his rejection of claims 113 to 121 under 35 U.S.C. §102(b) as being anticipated by Uhr et al. (U.S. Patent No. 5,686,072). Specifically, the Examiner states that Uhr et al. teach a method of treating a B cell malignancy, including leukemia and Non-Hodgkin's lymphoma, comprising administering to a patient a therapeutically effective amount of an anti-CD19 antibody and anti-CD22 immunotoxin. The Examiner further states that patients include humans and the combination can be administered intravenously.

Uhr et al. defines an immunotoxin as a conjugate comprising an antibody directed against a specific cell surface molecule that has been coupled to one or more toxin molecules (see, col. 4, lines 40-42). In regard to the toxin components of the immunotoxin, Uhr et al. states that included in the term "toxin" are the commonly designated toxins such as poisonous lectins, ricin, abrin, modeccin, botulina and diphtheria toxins, as well as other toxic agents such as radio-isotopes, cytotoxic and carcinostatic drugs and combinations of the various toxins that could also be coupled to one antibody molecule (see, col. 4, line 67 - col. 5, line 6). Preferred toxin components for use in Uhr et al. are the A chain portions of the above toxins, with ricin A chain being particularly preferred, and deglycosylated ricin A chain being even more particularly preferred (see, col. 5, lines 7-10).

Claims 113 to 121 have been replaced with new claims 150 to 172, which are directed to methods of treatment of a subject with a B-cell malignancy comprising administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate in which the anti-CD22 antibody comprises a light chain variable region comprising SEQ ID NO:19 and a heavy chain variable region comprising SEQ ID NO:27. Claims 151 to 172 depend from claim 150. Uhr et al. does not teach a method of treating a subject with a B-cell malignancy that comprises administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate in which the anti-CD22 antibody comprises a light chain variable region comprising SEQ ID NO:19 and a heavy chain variable region comprising SEQ ID

NO:27. The composition used in the claimed methods is not described in Uhr et al. nor is it inherent from Uhr et al.'s teachings. Applicants submit that Uhr et al. does not teach every element of the claimed inventions.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 113 to 121 as anticipated under 35 U.S.C. §102(b).

C. Third Rejection Under 35 US.C. §102(b)

The Examiner has maintained his rejection of claims 113 to 121 under 35 U.S.C. §102(b) as being anticipated by Goldenberg (U.S. Patent No. 6,183,744).

The Examiner states that Goldenberg teaches a method of treating a B cell malignancy in a patient comprising a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent, citing column 4, lines 25-26 and column 11, lines 5-8. The Examiner states next that Goldenberg teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (col. 11, lines 11-14), and that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias and acute lymphatic leukemias (col. 11, lines 8-11). The Examiner further states that regarding the therapeutic agent of the immunoconjugate, Goldenberg teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes and folic acid analogs. No enediyne compounds, such as calicheamicin, are mentioned in Goldenberg. The Examiner also notes that Goldenberg teaches that the immunoconjugates can be administered intravenously (col. 14, lines 8-15).

Claims 113 to 121 have been replaced with new claims 150 to 172, which are directed to methods of treatment of a subject with a B-cell malignancy comprising administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate in which the anti-CD22 antibody comprises a light chain variable region comprising SEQ ID NO:19 and a heavy chain variable region comprising SEQ ID NO:27. Claims 151 to 172 depend from claim 150. Goldenberg does not teach a method of

treating a subject with a B-cell malignancy that comprises administering to the subject a therapeutically effective dose of a composition comprising a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate in which the anti-CD22 antibody comprises a light chain variable region comprising SEQ ID NO:19 and a heavy chain variable region comprising SEQ ID NO:27. The composition used in the claimed methods is not described in Goldenberg nor is it inherent from Goldenberg's teachings. Applicants submit that Goldenberg does not teach every element of the claimed inventions.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 113 to 121 as anticipated under 35 U.S.C. §102(b).

Rejections under 35 U.S.C. §103(a)

Claims 124 to 127, 130 to 131, 133 and 142 to 143 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Goldenberg (U.S. Patent No. 6,183,744) in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588). Claims 134 to 135 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Goldenberg (U.S. Patent No. 6,183,744) in view of Trail et al. (Current Opinion in Immunology 1999, 11: 584-588), and in further view of Maloney et al. (Blood 1997, 90:2188-2195).

The Examiner states that the primary reference, Goldenberg, teaches a method of treating a B cell malignancy in a patient comprising a therapeutically effective amount of an anti-CD22 antibody immunoconjugate, wherein the immunoconjugate is a conjugate of an antibody component with a therapeutic agent, citing column 4, lines 25-26 and column 11, lines 5-8. The Examiner states next that Goldenberg teaches that anti-CD22 antibody immunoconjugates can be used to treat both indolent and aggressive forms of Non-Hodgkin's lymphoma (column 11, lines 11-14), and that the immunoconjugates are useful for the treatment of chronic lymphatic leukemias and acute lymphatic leukemias (column 11, lines 8-11). The Examiner further states that regarding the therapeutic agent of the immunoconjugate, Goldenberg teaches that useful therapeutic agents for the preparation of the immunoconjugate include, but are not limited to, cancer chemotherapeutic drugs such as nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes and folic acid analogs.

The Examiner acknowledges that Goldenberg does not explicitly teach that the therapeutic agent can be calicheamicin as in the conjugates employed in the methods of claims 124 to 127, 129 to 135 and 142 to 143. The Examiner states that the Trail et al. article teaches monoclonal antibody drug conjugates in the treatment of cancer. The Examiner further states that specifically, the reference teaches that members of the enediyne family of antibiotics such as calicheamicin are among the most toxic antitumor compounds described to date, but their utility as antitumor drugs has for the most part been limited by their low therapeutic index. Finally, the Examiner states that this cited reference further teaches that antibody directed delivery provides a potential means to exploit the potency of these compounds while minimizing their systemic toxicity. The Examiner asserts that one of ordinary skill in the art would have a reasonable expectation of success that by administering a conjugate comprising calicheamicin and an anti-CD22 antibody to a subject with a B-cell malignancy, one would achieve an effective method of treatment.

The Examiner relies on Goldenberg in view of Trail et al. and further in view of Maloney et al. to reject claims 134 and 135. The Examiner states that Maloney et al. teach a method of treating low-grade Non-Hodgkin's lymphoma by administering to a patient a therapeutically effective amount of Rituximab. The Examiner asserts that it would have been prima facie obvious to combine the method of treating Non-Hodgkin's lymphoma by administering an immunoconjugate comprising an anti-CD22 antibody taught by Goldenberg in view of Trail et al. with Rituximab in view of Maloney et al.'s teachings.

Applicants respectfully disagree with the Examiner's rejections. Applicants' arguments submitted in the Amendment and Response filed December 21, 2007 are incorporated by reference herein and will not be restated here. Applicants reiterate that it is not routine practice to treat a subject with a B-cell malignancy by administering a composition comprising a cytotoxic drug-anti-CD22 antibody conjugate, including a calicheamicin-anti-CD22-antibody-conjugate, alone or with one or more cytotoxic or bioactive agents.

Claims 124 to 127, 129 to 135 and 142 to 143 and been replaced with claims 150 to 256 of the present application, which are directed to:

(1) methods of treating a subject with a B-cell malignancy comprising administering to the subject a therapeutically effective dose of a composition comprising a therapeutically

effective dose of a monomeric cytotoxic drug derivative/anti-CD22 antibody conjugate in which the anti-CD22 antibody comprises:

a. a light chain variable region comprising SEQ ID NO:19 and a heavy chain variable region comprising SEQ ID NO:27 (**Claims 150 to 172**);
b. a light chain variable region comprising SEQ ID NO:28 and a heavy chain variable region comprising SEQ ID NO:30 (**Claims 173 to 195**);
c. SEQ ID NO: 1 for CDR-H1, SEQ ID NO: 2 or SEQ ID NO: 13 or SEQ ID NO: 15 or SEQ ID NO: 16 or residues 50-65 of SEQ ID NO: 27 for CDR-H2, SEQ ID NO: 3 for CDR-H3, SEQ ID NO: 4 for CDR-L1, SEQ ID NO: 5 for CDR-L2 and SEQ ID NO: 6 for CDR-L3 (**Claims 196 to 218**); or
d. a light chain variable region comprising SEQ ID NO:7 and a heavy chain variable region comprising SEQ ID NO:8 (**Claims 219 to 241**); and

(2) methods of treating a subject with aggressive lymphomas comprising administering to the subject a therapeutically effective dose of a composition comprising a therapeutically effective dose of a monomeric calicheamicin derivative-anti-CD22 antibody conjugate, which comprises a calicheamicin derivative functionalized with 3-mercapto-3-methyl butanoyl hydrazide and an anti-CD22 antibody comprising SEQ ID NO:1 for CDR-H1, SEQ ID NO: 2 or SEQ ID NO:13 or SEQ ID NO:15 or SEQ ID NO:16 or residues 50-65 of SEQ ID NO:27 for CDR-H2, SEQ ID NO:3 for CDR-H3, SEQ ID NO:4 for CDR-L1, SEQ ID NO:5 for CDR-L2, and SEQ ID NO:6 for CDR-L37 (**Claims 242 to 256**).

Neither Goldenberg in view of Trail et al. or further in view of Mahoney et al. teach or suggest a method of treating a subject with a B-cell malignancy by administering a composition comprising a cytotoxic drug derivative/anti-CD22-antibody conjugate using the claimed anti-CD22 antibodies described above alone or in combination with one or more cytotoxic or bioactive agents. Applicants respectfully submit that the Examiner has not made a prima facie case of obviousness.

By reason of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 124 to 127, 129 to 133 and 142 to 143 and the rejection of claims 134 to 135 as obvious under 35 U.S.C. §103(a).

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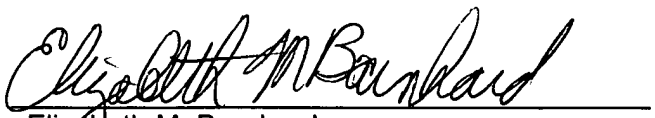
In view of the foregoing discussion, applicants submit that the present application is in condition for allowance. Reconsideration and allowance are respectfully requested.

If a telephone conference would advance prosecution of this application, the Examiner is invited to telephone the undersigned at (845) 602-1842.



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